SYNOPSIS

SYNOPSIS

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Name of the Student	: CHIRAG GIRISHKUMAR NAIK
Name of Guide	: Dr. G .M. MALIK
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The present work entitled, "SYNTHESIS, CHARACTERIZATION AND ANTIBACTERIAL ACTIVITY OF SOME HETEROCYCLIC COMPOUNDS BASED ON COUMARIN AND PYRAZOLONE" has been divided in five chapters.

Chapter-1 Gives brief introduction and review of literature on the synthetic and pharmaceutical applications of heterocyclic compound.

To explore the history of heterocyclic chemistry it is necessary to go back to 1800's, when heterocyclic chemistry entered as a dot on horizon of science. There was a big explosion during world war-II in the field of research of heterocyclics. Chemistry of heterocyclic compounds have been one of the most complex and intriguing branch of organic chemistry. Heterocyclic compounds contribute more than fifty percent of compounds recorded in chemical abstracts; these compounds constitute the largest and most varied family of organic compounds. In morden organic chemistry, medicinal chemistry and biochemistry various broader aspects of heterocyclic chemistry are recognised as disciplines of general significance that touch almost all aspects. Heterocyclic compounds exhibit a high degree of structural variation and have proven to be broadly and economically useful as therapeutic agents.

According to encyclopaedia Britannica "Any of a class of organic compounds whose molecules contain one or more rings of atoms with at least one atom (the hetero atom) being an element other than carbon, most frequently oxygen, nitrogen or sulphur" A ring consisting of only one kind of atom i.e carbon is called homo cyclic ring while heterocyclics are counter parts of homocyclic compounds. A branch of chemistry dealing with synthesis, properties and applications of heterocycles is called as heterocyclic chemistry and is divided broadly in two groups aromatic heterocyclics and non aromatic heterocyclics.

Stable ring structures which is not easily hydrolysable and do not de-polymerized easily is a usual feature of heterocyclic compounds. The heterocyclics having one hetero atoms, in general is stable, those having two heteroatom are more likely to occurs reactive intermediates but heterocycles with three atoms in a ring are more reactive because of ring strain. The roles of heterocyclic compounds in biological process are very vital and are widely spread in nature. The heterocyclics are commonly found in nature in nucleic acids, plant, alkaloids, anthocyanins and flavones, also in heam and chlorophyll. Apart from these some vitamins, proteins, hormones posses aromatic heterocyclic system. To cater the increasing demand of various heterocyclic compounds manmade heterocycles designed by organic chemists are supplied in the market which are used as pharmaceuticals, agrochemicals, dyes, sweeteners, perfumes etc. They have become rather inevitable part of human life.

Chapter -2: deals with the synthesis of coumarin derivatives.

Coumarin derivatives are present in significant quantity in plants and more than 1300 coumarins were identified from natural sources[1], which serve as important model for advanced design and synthesis of more active analogous coumarins that natural compounds possess were shown to have potent antioxidant and radical- scavenging properties in various experimental models[2]. Coumarin is derived from 'coumarou' the vernacular name of the Tonka bean (*Dipteryx odorata willd, Fabaceae)*, from which coumarin itself was isolated in 1820[4]. They are the family of lactones containing benzopyrone skeletal framework that have enjoyed isolation from plant as well as total synthesis in the laboratory.

There are large numbers of coumarins having biological activities such as anticoagulant, antibacterial, antifungal, insecticidal etc. Bucumolol, Chromonar, Folescutol

and 4-methyl umbeliferon are coumarin derivatives and clinically used as antiarhythmic, vasodilator, capillary protectant and antispasmodic, respectively. Warfarin and acenocoumarol, which are coumarin derivatives, exhibit anticoagulant activity[12].

The synthesis of coumarin and its derivatives have attracted considerable attention from organic and medicinal chemists for many years as a large number of natural products contain these heterocyclic nucleus[3]. They are widely used as optical brighteners[5] and dispersed fluorescent and laser dyes[6] , additives in food, perfumes, cosmetics, and pharmaceuticals[4]. There for the that synthesis of this heterocyclic nucleus is of much interest. Coumarins have been synthesized by several routes including Pechmann[7], Perkin[8], Knoevenagel[9], Reformatsky[10] and Wittig reactions[11].

The synthesis of heterocyclic compounds of coumarin derivatives, which were synthesized by using various types of pyrazolone, thiazole and piprazine benziso thiazole derivatives to react with 4-hydroxy coumarin have been divided in four sections.

Section-I describes the synthesis of 4-(4-hydroxy-2-oxo-2H-chromen-3-yl)-3-methyl-1substituted-phenyl-pyrazol-5(4H)-one derivative.

4-hydroxy coumarin(1.0 mole), various pyrazolone derivatives(1.0 mole) and potassium carbonate(1.5 mole) were added to solvent dimethyl formamide maintaining different temp and refluxing for different time durations which yielded coumarin derivatives.

Section-II discusses the synthesis of ethyl 4,5-dihydro-2-(4-(3-alkane -4-hydroxy coumarin)phenyl)-4-methylthiazole-5-carboxylate

4-hydroxy coumarin(1.0 mole), various thiazole derivatives(1.1 mole) and potassium carbonate(1.5 mole) in solvent as a dimethyl formamide were refluxed, temperature and time was adjusted and maintained according the reaction.

Section-III details the synthesis of ethyl 2-(4-(3-alkane-4-hydroxy coumarin)-3-formylphenyl)-4,5-dihydro-4-methylthiazole-5-carboxylate

4-hydroxy coumarin(1.0 mole), various thiazole derivatives(1.1 mole) and potassium carbonate(1.5 mole) in solvent dimethyl formamide were reacted maintaining necessary tempture and reaction time to obtain various coumarin derivatives.

Section-IV describes the synthesis of 3-(5-(4-(benzo[d]isothiazol-3-yl)piperazin-1-yl)alkyl)-4-hydroxy-2H-chromen-2-one

4-hydroxy coumarin(1.0 mole), different piprazine benziso thiazole derivatives(1.1 mole) and potassium carbonate(1.5 mole) were added in solvent dimethyl formamide, the temperature and reaction period adjusted depending upon piprazine benziso thiazoles.

Chapter-3 describes synthesis of pyrazolone derivatives.

Nitrogen containing heterocycles like pyrazolines received considerable attention in recent years due to their broad spectrum of biological activities[13]. Azole unit in association with other moieties like halophenyl in the pyrazoles is an essential pharmacophore of a number of well known antifungal agents[14]. Pyrazolines/ pyrazoles with sulphonamide moiety are found to be biologically active.

Pyrazolones are important class of heterocyclic compounds that is found in many drugs and is nonsteroidal anti-inflammatory agent used in the treatment of arthritis and other musculoskeletal and joint disorders. Pyrazolones are biologically important group of compounds having different activities like antibacterial, antifungal, antiinflammatory, antidiabetic, analgesic, antipyretic, immune suppressive agents, hypoglycemic, antiviral, antineoplastic activity and other biological activities [15, 16]. Pyrazolone derivatives are of particular importance in pharmaceutical chemistry due to their numerous applications as analgesic, antipyretic, antiarthritic, uricosuric, anti-inflammatory and antiphlogistic properties [17,18].

Pyrazolopyrimidine derivatives have received a great deal of attention due to their pharmacological activity[19], such as allopurinol[20], which is still the drug of choice for the treatment of hyperurecemia and gouty arthritis[21].

Pyrazolone derivatives were synthesized by reacting various type of thiazole with different piprazine benziso thiazole, chloroacetyl chloride and their condensation with urea, thiourea,2-amino-5-methyl pyridine. Which is divided in three sections.

Section-I describes the synthesis of various pyrazolone derivatives.

Pyrazolone derivative (1.0 mole), chloroactylchloride (1.1 mole) and potassium carbonate (1.5 mole) in solvent acetone were refluxed maintaining suitable temperature and process to yield pyrazolone derivative these derivatives of pyrazolone reacted with urea, thiourea and 2-amino -5- methyl pyridine in presence of sodium carbonate with suitable solvent media at different temperature to obtain various pyrazolone derivatives.

Section-II describes the synthesis of ethyl 4,5-dihydro-2-(4-(1-alkane - 3-methyl pyrazol-5(4H)-one)phenyl)-4-methylthiazole-5-carboxylate

Ethyl 4,5-dihydro-2-(4-hydroxyphenyl)-4-methylthiazole-5-carboxylate derivative(1.0 mole) , piprazine derivative(1.05 mole) and potassium carbonate(1.05 mole) in dimethyl formamide as a solvent maintaining required temperature and time duration for different reactions were refluxed to obtain various pyrazolone derivatives.

Section-III deals with the synthesis of ethyl 2-(3-formyl-4-(1-alkane - 3-methyl pyrazol-5(4H)-one)phenyl)-4,5-dihydro-4-methylthiazole-5-carboxylate

Ethyl 2-(3-formyl-4-hydroxyphenyl)-4,5-dihydro-4-methylthiazole-5-carboxylate derivative(1.0 mole) , piprazine derivative(1.05 mole) and potassium carbonate(1.05 mole) using dimethyl formamide as solvent and maintaining different temperature and reaction time for different piprazines which yielded pyrazolone derivatives.

Chapter-4: Synthesis of thiazoles has been given in this chapter.

Thiazoles constitute an important class of compounds. Their chemistry and biological potency has been widely investigated and extensively reviewed[22] in the past years. Thiazoles have special place in the field of heterocyclic chemistry because of their diversified activities like anticancer[23,24], antitumor[25], antiviral[26], local anaesthetic[27], antiarrhythmic[28], antihypertensive[29], antibacterial[30], anti-inflammatory[31], antifungal[32] and antisecretory[33]. They are also used as sodium channel blocker[34].

Heterocyclic compounds of 4-hyrdoxy thiazole, 3-formyl-4-hyrdoxy thiazole derivative were synthesized by using various type of 2-3-dichloro phenyl piprazine hydrochloride and piprazine benziso thiazole reacting with 4 –hyrdoxy thiazol and 3-formyl-4-hyrdoxy thiazole. The synthesis of thiazole derivatives has been divided in four sections.

Section-I describes the synthesis of ethyl 2-(4-(5-(4-(2,3-dichlorophenyl)piperazin-1-yl) alkeneoxy)-3-formylphenyl)-4,5-dihydro-4-methylthiazole-5-carboxylate.

Ethyl 2-(3-formyl-4-hydroxyphenyl)-4, 5 – dihydro - 4-methylthiazole – 5 - carboxylate derivative(1.0 mole), piprazine derivative (in calculated mole proportion), potassium carbonate (in calculated mole proportion) and dimethyl formamide as a solvent media maintaining different temperature and suitable time duration were reacted to obtain various thiazole derivatives.

Section-II describes the synthesis of ethyl 2-(4-(5-(4-(2,3-dichlorophenyl)piperazin-1-yl)alkeneoxy)phenyl)-4,5-dihydro-4-methylthiazole-5-carboxylate.

Ethyl 4,5-dihydro-2-(4-hydroxyphenyl)-4-methylthiazole-5-carboxylate derivative(1.0 mole) , piprazine derivative (in calculated mole proportion), potassium carbonate (in calculated mole proportion) and dimethyl formamide as a solvent maintaining different temperature and suitable time duration were reacted to obtain various thiazole derivatives.

Section-III describes the synthesis of ethyl 2-(4-((4-(benzo[d]isothiazol-3-yl)piperazin-1-yl)alkoxy)phenyl)-4,5-dihydro-4-methylthiazole-5-carboxylate

Ethyl 4,5-dihydro-2-(4-hydroxyphenyl)-4-methylthiazole-5-carboxylate derivative(1.0 mole) , piperazine benziso thiazole derivative (in calculated mole proportion), potassium carbonate (in calculated mole proportion) and dimethyl formamide as a solvent media maintaining different temperature and suitable time duration were reacted to obtain various thiazole derivatives.

Section-IV describes the synthesis of ethyl 2-(4-((4-(benzo[d]isothiazol-3-yl) piperazin-1-yl)alkoxy)-3-formylphenyl)-4,5-dihydro-4-methylthiazole-5-carboxylate.

Ethyl 2 - (3-formyl-4-hydroxyphenyl) - 4,5 – dihydro - 4-methylthiazole- 5 - carboxylate derivative(1.0 mole) , piperazine benziso thiazole derivative (in calculated mole proportion), potassium carbonate (in calculated mole proportion) and dimethyl formamide as a solvent maintaining different temperature and suitable time duration were reacted to obtain various thiazole derivatives.

Chapter-5: This chapter describes the synthesis of indan derivatives.

Indan derivatives are commonly used intermediates in pharmaceutically active substances. Rasagiline, a derivative of 1-amino indan is a useful anti-parkinsonion agent. Enantiomerically pure (1S, 2R)-1-amino-2-indanol 1 is used as a chiral auxiliary[35,36] for asymmetric synthesis and an important component of indinavir 2, a potent inhibitor of the protease of human immunodeficiency virus[37] (HIV).

The chapter presents the work related to the synthesis of heterocyclic compounds of indan derivatives, which were synthesized by using various types of thiazole and piprazine benziso thiazole.

Section-I describes the synthesis of (R)-2,3-dihydro-N-(prop-2-ynyl)-1(ethyl 4,5-dihydro-2-(4-alkenoxyphenyl)-4-methylthiazole-5-carboxylate)-inden-1-amine

R-(+)-N-propargyl-1-aminoindan derivative(1.0 mole) was reacted with thiazole derivatives, in presence of potassium carbonate and solvent dimethyl formamide for solvent media maintaining different temperature and suitable time duration, were reacted to obtain various indan derivatives.

Section-II describes the synthesis of (R)-2,3-dihydro-N-(prop-2-ynyl)-1(ethyl 2-(3-formyl-4-alkaneoxyphenyl)-4,5-dihydro-4-methylthiazole-5-carboxylate)-inden-1-amine

R-(+)-N-propargyl-1-aminoindan derivative(1.0 mole) was reacted with thiazole derivatives, in presence of potassium carbonate and solvent dimethyl formamide for solvent media maintaining different temperature and suitable time duration, were reacted to obtain various indan derivatives.

Section-III describes the synthesis of (R)-2,3-dihydro-N-(prop-2-ynyl)-1(3-(4-(alkane)piperazin-1-yl)benzo[d]isothiazole)-inden-1-amine

R-(+)-N-propargyl-1-aminoindan derivative(1.0 mole) was reacted with piprazine benziso thiazole derivatives, in presence of potassium carbonate and solvent dimethyl formamide for solvent media maintaining different temperature and suitable time duration, were reacted to obtain various indan derivatives.

The heterocyclic compounds synthesised in chapters 2 to 5 has been characterised by, IR, H NMR, Mass spectra and elemental analysis. The synthesised compound were screened for their antimicrobial activity.

Infrared spectral studies

Infrared spectroscopy of synthetic hetrocyclic compounds described in chapters 2 to 5 have been studied out for the structural elucidation of particular functional groups present in organic molecules using FTIR spectrophotometer Perkin Elmer RX-1 using KBR pellets.

H NMR spectra

Nuclear Magnetic Resonance (NMR) spectroscopy of some selected synthesised heterocyclic compounds described in chapters 2 to 5 have been studied Sophisticated multinuclear FT NMR spectrometer model Avance-II (Bruker) using TMS as internal standard in DMSO and chloroform solvent.

Mass spectra

The mass spectrum of selected compounds in chapters 2 to 5 have been studied by Waters Micromass Q-Tof Micro . This Instrument is hybrid quadrupole time of flight mass spectrometer equipped with electrospray ionization (ESI) and atmospheric pressure chemical ionization (APcI) sources having mass Range of 4000 amu in quadruple and 20000 amu in ToF. The molecular ion peak and the base peak in all compounds were clearly obtained in mass spectrum study. The molecular ion peak (M^+) values are in good agreement with molecular formula of all the compounds synthesized.

C, H, N analysis

Elemental analysis of the compounds was carried out on Perkin Elmer PE-2400 series II at SICART, Vidyanagar and the results were in agreement with the structures assigned.

Antimicrobial activity

It accommodates the biological screening of the compounds prepared in chapter 2 to 5. The synthesized compounds were screened for their antimicrobial activity from measuring zone of inhibition in mm. All the compounds were screened for their in vitro antimicrobial activity against different bacterial strains such as Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus and fungi Candida albicans. Standard drugs like Amicillin and Amphoterecin-B were used for the comparison purpose.

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Chirag .G. Naik
CANDIDATE

Dr. G .M. Malik
SUPERVISOR

Date:- 14-05-2013.

Dr. G. M. MALIK
Head, Dept. of Chemistry,
Navyug Science College,
Rander Road, SURAT-9.